HM | RJS | Elaine

**PATENT COOPERATION TREATY**

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
DAVID J. LEVY
GLAXOSMITHKLINE
FIVE MOORE DRIVE
PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 31 JAN 2006 |
| Applicant's or agent's file reference<br>PR60375WO | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US04/35129 | 22 October 2004 (22.10.2004) | 28 October 2003 (28.10.2003) |

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 9/14; A01N 25/02, 25/00 and US Cl.: 424/489, 43, 46; 514/826, 951

Applicant

GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/ US | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (571) 273-3201 | 11 December 2005 (11.12.2005) | S. Gollamudi<br>Telephone No. (703) 308-0196 |

Form PCT/ISA/237 (cover sheet) (April 2005)

Docket No: PR60375WO
Attorney: RJS
Paper: Written Opinion
Due Date: 31 Mar 2006
Deadline:
Recorded:

RECEIVED
FEB 06 2006
GLAXOSMITHKLINE
CPI / RTP

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/35129

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/35129

**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |
| Inventive step (IS) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |
| Industrial applicability (IA) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |

2. Citations and explanations:

Please See Continuation Sheet

**Supplemental Box**
In case the space in any of the preceding boxes is not sufficient.

**V.1. Reasoned Statements:**
The opinion as to Novelty was positive (Yes)with respect to claims 9-10, 13, 15, 29-30, 33, 35, 38, 48-49, 52, 54, 57
The opinion as to Novelty was negative (No) with respect to claims 1-8, 11-12, 14, 16-18, 19-28, 31-32, 34, 36-37, 39-47, 50-51, 53, 55, 56
The opinion as to Inventive Step was positive (Yes)with respect to claims NONE
The opinion as to Inventive Step was negative(NO) with respect to claims 1-57
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-57
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

**V. 2. Citations and Explanations:**

Claims 1-8, 11-12, 14, 16-17, 19-28, 31-32, 34, 36-37, 39-47, 50-51, 53, 55, 56 lack novelty under PCT Article 33(2) as being anticipated by Yang (6,495,167).

Yang discloses the production of unique agglomerated dosage forms for administration of pharmacologically active agents to patients. The formulations in accordance with this invention are particularly well suited for oral and/or nasal inhalation. See abstract. Yang discloses the invention improves the ability to administer fine powdered medicaments is by the inclusion of dry lactose (amorphous lactose-binder). The binder provides free flowing characteristics to the powder, storage stability, and strength. See column 10, lines 55-65.

Yang discloses the pharmacologically active agent or drug is a material capable of being administered in a dry powder form to the respiratory system, including the lungs. Particularly preferred pharmacologically active agents in accordance with the present invention include corticosteroids such as: mometasone furoate; beclomethasone dipropionate; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; .beta.-agonists) including salbutamol (albuterol), terbutaline, salmeterol, and bitolterol may also be administered. Yang discloses formoterol has a highly selective long-lasting .beta..sub.2 -adrenergic agonist having bronchospasmolytic effect, is effective in the treatment of reversible obstructive lung ailments of various genesis, particularly asthmatic conditions. The salts, esters, and solvates of the above compounds may be used. See column 9, lines 25-65. Further, Yang discloses the "drug" utilized in the compositions are either single pharmaceutical active or a combination of actives, including a beta-agonist and a corticosteroid. See column 10, lines 1-10.

Figure 1 discloses mometasone: anhydrous lactose in a ratio of 1:5.8 and measure the moisture uptake at a relative humidity of 25 degrees Celsius.

Yang discloses agglomerates are useful in commercially available dry powder aerosol inhalers including Schering's inhaler as identified above, Diskhaler (Allen & Hanburys), Accuhaler (Allen & Hanburys), Diskus (Glaxo), Spiros (Dura), Easyhaler (Orion), Cyclohaler (Pharmachemie), Cyclovent (Pharmachemie), Rotahaler (Glaxo), Spinhaler (Fisons), FlowCaps(Hovione), Turbospin (PH&T), Turbohaler (Astra), EZ Breath (Norton Healthcare/IVAX), MIAT-HALER (Miat), Pulvinal (Chiesi), Ultrahaler (Fisons/Rhone Poulenc Rorer), MAG-Haler (GGU), Prohaler (Valois), Taifun (Leiras), JAGO DPI (JAGO), M L Laboratories' DPI (M L Laboratories). See column 15, lines 55-65.

Claims 9-10, 13, 15, 18, 29-30, 33, 35, 38, 48-49, 52, 54, and 57 lacks an inventive step under PCT Article 33(3) as being obvious over Yang (6,495,167).

The teachings of Yang have been delineated above.

**Supplemental Box**
In case **the space in any of the preceding boxes is not sufficient**.

Yang does not specify the instant derivatives of salmeterol, salbutamol, and fluticasone or the use of an additional additive.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the instant derivatives since Yang teaches any suitable derivatives of the pharmaceutical actives may be used. It would have been further obvious to a skilled artisan to add other conventional excipients to the formulation as routinely done in the pharmaceutical art.

Claims 1-6 and 18-21 lack novelty under PCT Article 33(2) as being anticipated by Leibovici et al (6,482,417).

Leibovici discloses a powder composition comprising 25.5-65% lactose anhydrous, torsemide modification II (diuretic), microcrystallines cellulose, povidone, and crospovidine. See column 4, lines 40-60 and Table 1. Note "suitable for inhalation" is not given patentable weight since it does not impart a structural limitation on the composition itself.

Claims 1-57 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in the pharmaceutical art.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

**The following examples illustrate the manner in which amendments must be explained in the accompanying letter:**

1 [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2 [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." **or**
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4 [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

**"Statement under Article 19(1)" (Rule 46.4)**

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

**Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

**Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.